Dapagliflozin is associated with improved glycaemic control and weight reduction at 44 months of follow-up in a secondary care diabetes clinic in the UK

Natasha Shrikrishnapalasuriyar BMedSci, MB BS, MRCP[1], Ayesha Shaikh MB BS[1], Aliya Mohd Ruslan MBChB, MRCP[1], Giselle Asharaf MBBS, MRCP[1], Maneesh Udiawar MD, FRCP[1], David E Price MA, MD, FRCP[1], Jeffrey W Stephens BSc, MB BS, PhD, FRCP[11,2].

[1]Department of Diabetes and Endocrinology, Morriston Hospital, Swansea Bay University Health Board, Swansea SA6 8NL, UK

[2]Diabetes Research Group, Swansea University Medical School, Swansea University, Swansea, SA2 8PP, UK.

Correspondence to:

Professor Jeffrey Stephens, Diabetes Centre, Morriston Hospital, Swansea, SA6 6NL. UK

Email: J.W.Stephens@Swansea.ac.uk

Tel: +44(0)1792704078

Keywords: Dapagliflozin; SGLT2 inhibitor; HbA1c; Cardiovascular.

Conflict of Interests:

Professor Stephens has received research funding from Astra Zeneca for different work along with speaker fees.

Highlights

1. Dapagliflozin provides effective glycaemic control over a median of 44 months without deterioration in renal function.
2. Weight loss was maintained with therapy during the treatment period.
3. This supports maintained benefits associated with dapagliflozin during follow-up in routine clinical practice.

Abstract

Background and aims

We examined HbA1c and cardiovascular risk factors with a median follow-up of 44 months therapy with dapagliflozin.

Methods

We undertook a clinical practice evaluation of 101 patients attending our clinic.

Results

Dapagliflozin resulted in a significant reduction in HbA1c 82.6 ±15.7 v 68.7 ±17.8 mmol/mol.

Conclusion

Dapagliflozin maintains glycaemic control along with sustained improvements in weight and no decline in renal function.

Introduction

Sodium glucose co-transporter 2 inhibitors (SGLT-2i) improve glycaemic control, blood pressure, weight, and the decline in the onset of chronic kidney disease, cardiovascular events and heart failure. SGLT-2i have beneficial effects in the clinical trial [1-3] and the real-world setting [4-6]. There is debate relating to the validity of cardiovascular outcome trials [7] and the real-world trials [8] to routine practice. We describe our real-life clinical experience of dapagliflozin in secondary care with a median treatment duration of 44 months (range 36-82 months).

Methods

Subjects

The work was undertaken as a routine evaluation of clinical practice. A total of 101 patients with a pre-existing clinical diagnosis of type 2 diabetes mellitus (T2DM) were identified from our local secondary care electronic database that had treatment with dapagliflozin and had at least three years of follow-up data. The aim was to examine HbA1c, weight, body mass index (BMI), blood pressure, serum lipids, serum creatinine and estimated glomerular filtration rate (eGFR) and the urinary albumin: creatinine ratio (UACR) during follow-up.

Statistical Analysis

Paired t-tests were used to compare HbA1c, weight, BMI, blood pressure, cholesterol, LDL-cholesterol, HDL-cholesterol, creatinine and eGFR. The mean and standard deviation were used to describe these variables. UACR and triglycerides did not have a normal distribution and are described with the median and interquartile range, with analysis being undertaken using Wilcoxon signed rank tests.

Results

Baseline Characteristics

At baseline, the mean age was 61 ±10 years, HbA1c 82.6 ±15.7 mmol/mol, weight 106 ±21 kg, BMI 37 ±7 kg/m^2. The sample comprised of 101 patients (43 males, 58 females) with a median duration of diabetes of 12 years (interquartile range 8-12) and a median duration of dapagliflozin treatment of 44 months (range 36-82).

Prior to dapagliflozin, there was considerable treatment heterogeneity. As shown in figure 1, 35 patients received a combination of insulin with or without oral agents; 20 patients were taking glucagon like peptide-1 receptor agonists (GLP-1RA) with or without oral agents; 11 patients received a combination of GLP-1RA and insulin (as two injections or as xultophy) with or without oral agents; and 35 patients received oral therapies alone. Oral therapies consisted of combinations of metformin, sulphonylurea and dipeptidyl peptidase-4 (DPP-4) inhibitors.

Changes in clinical measures associated with dapagliflozin

Improvements in glycaemic control and weight were observed at follow-up. As shown in table 1, mean HbA1c prior to dapagliflozin was 82.6 ±15.7 mmol/mol and 68.7 ±17.8 mmol/mol following the addition of dapagliflozin ($p<0.0001$). The mean reduction in weight and BMI were -7 kg and -3 kg/m^2 respectively ($p<0.0001$). No decline was observed in eGFR and UACR. Ten patients had an episode of an acute coronary syndrome.

We chose *a priori* to divide the sample by the mean baseline HbA1c (83 mmol/mol) to examine response status by HbA1c at 6 months. We observed a greater reduction in HbA1c in the higher HbA1c group (-22.9 mmol/mol compared to -5.5 mmol/mol). In those with a HbA1c >83 mmol/mol, the pre and post dapagliflozin HbA1c were 95.6 ±9.6 and 72.7 ±19.6 mmol/mol respectively (p<0.001). In those with HbA1c ≤83 mmol/mol, the pre and post dapagliflozin HbA1c were 70.7 ±9.5 and 65.2 ±15.1 mmol/mol respectively (p=0.009).

Changes related to baseline medication

As shown in table 2, those who received a combination of insulin with or without oral agents at baseline had significant improvements in HbA1c (-10.6 mmol/mol, p=0.01), weight (-4.2 kg, p=0.007) and BMI (-2.4 kg/m^2, p=0.025). The total daily insulin dose was unchanged. For the patients receiving a GLP-1RA with or without oral agents at baseline, significant improvements were observed in HbA1c (-17.8 mmol/mol, p<0.0001), weight (-3.2kg, p<0.0001) and BMI (-4.2 kg/m^2, p<0.0001). For patients taking a combination of a GLP-1RA and insulin with or without oral agents there was a significant improvement in HbA1c (-20.7 mmol/mol, p<0.0001). In those receiving oral therapy, dapagliflozin was associated with significant reductions in HbA1c (-12.7 mmol/mol, p<0.0001), weight (-8.2 kg, p<0.0001) and BMI (-3.4 kg/m^2, p<0.0001).

Discussion

SGLT-2i improve HbA1c, weight, cardiovascular risk and renal outcomes [1-6]. We describe real-world experience in a complex group of secondary care patients receiving combinations of diabetes therapies. Beneficial effects were seen on HbA1c, weight, and BMI, and no reduction was observed in eGFR after a median of

44 months. Dapagliflozin was associated with a maintained greater reduction in glucose in those with a higher HbA1c. The reduction in HbA1c was also observed in all therapy groups. Of interest there was a greater reduction in weight and BMI in those patients who received a GLP-1RA. This is in line with real-world studies were patients received treatment with GLP-1RA and an SGLT2i for up to 6 months [9] and a meta-analysis where participants were treated for up to 1 year [10]. Within the sample 10/101 had evidence of an acute coronary syndrome during follow-up. There was no significant decline observed in renal function.

This study provides further real-world data demonstrating maintained benefits of dapagliflozin. Within the real-world, the available literature reports benefits up to 18 months [11] and within the clinical trials up to 4 years [12]. We acknowledge that this study is limited by examining a sample of secondary care patients with a small number at follow-up. Nevertheless, the data should reassure the clinician that SGLT2i maintain efficacy in a complex sample treated with many different diabetes therapies. Our results are consistent with the observation that there is generalisability in patients with type 2 diabetes for benefit from SGLT2i [13]. A recent study examined the different baseline characteristics of patients who were initiated on dapagliflozin and suggested that this may influence patient outcomes. Whilst we saw differences relating to weight and BMI in different therapy groups, the effect on HbA1c appeared to be consistent [8].

Funding

No funding was required for this work.

Author contributions

NS, AS, AR, GS and JS collected and reviewed the data for analysis. JS conducted the statistical analysis. MU, DP, JS, NS, AR, AS and GS all contributed to the preparation and review of the manuscript.

Table 1: Changes in clinical measures following three years of therapy with dapagliflozin

Measurements	Pre dapagliflozin	Post dapagliflozin	P value
HbA1c (mmol/mol)	82.6 (15.7)	68.7 (17.8)	<0.0001
HbA1c (%)	9.7 (1.4)	8.4 (1.6)	
Weight (kg)	106 (21)	99 (19)	<0.0001
BMI (kg/m^2)	37 (7)	34 (7)	<0.0001
Systolic blood pressure (mmHg)	140 (18)	139 (20)	0.81
Diastolic blood pressure (mmHg)	81 (10)	78 (9)	0.02
Cholesterol (mmol/L)	4.5 (1.5)	4.0 (1.0)	<0.0001
LDL-cholesterol (mmol/L)	2.1 (1.0)	2.8 (0.8)	0.001
HDL-cholesterol (mmol/L)	1.4 (0.9)	1.2 (0.3)	0.06
Triglyceride (mmol/L) *	1.8 [1.3-2.6]	1.8 [1.3-2.7]	0.78
Creatinine (µmol/L)	71 (15)	74 (19)	0.09
eGFR (mL/min per 1.73 m^2)	95 (22)	93 (24)	0.20
Urine ACR (mg/mol) *	1.9 [0.8-7.3]	3.1 [1.2-7.9]	0.29

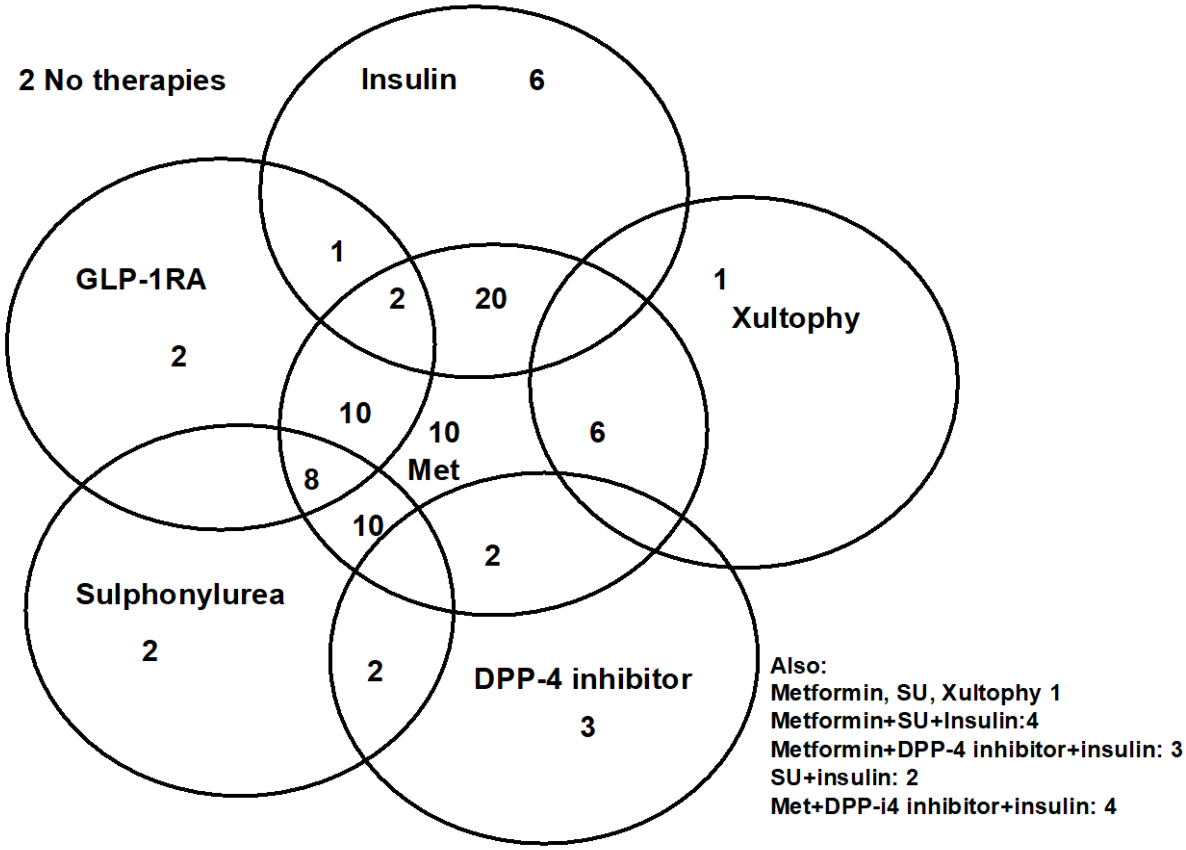
UACR: Urine albumin: creatinine ratio. eGFR: estimated glomerular filtration rate. BMI: Body mass index. Mean and standard deviation shown for normal data and analysed by paired t-test. *The median and interquartile range represents with data without a normal distribution. Analysis performed by Wilcoxon signed Ranks test.

Table 2: The impact of previous therapy on dapagliflozin response at 3 years follow-up

Measurement	Pre dapagliflozin	Post dapagliflozin	P value
Patients previously using insulin (n=35)			
HbA1c (mmol/mol)	85.3 (14.1)	74.7 (21.1)	0.01
HbA1c (%)	10 (1.3)	9.0 (1.9)	
Weight (kg)	100.9 (20.5)	96.7 (18.5)	0.007
BMI (kg/m^2)	34.9 (5.9)	32.5 (8.0)	0.025
Insulin total daily dose (units)	72 (41)	74 (41)	0.42
Patients previously using GLP-1 analogues (n=20)			
HbA1c (mmol/mol)	83.6 (16.0)	65.8 (15.5)	<0.0001
HbA1c (%)	9.8 (1.5)	8.2 (1.4)	
Weight (kg)	101.1 (17.9)	97.9 (17.0)	<0.0001
BMI (kg/m^2)	37.8 (7.2)	33.6 (6.0)	<0.0001
Patients previously using GLP-1 analogues and insulin (n=11)			
HbA1c (mmol/mol)	85.9 (19.8)	65.2 (16.3)	<0.0001
HbA1c (%)	10.0 (1.8)	8.1 (1.5)	
Weight (kg)	110.8 (17.7)	111.1 (13.5)	0.91
BMI (kg/m^2)	37.1 (4.8)	37.4 (4.3)	0.77
Patients previously on oral therapies/no therapy (n=35)			
HbA1c (mmol/mol)	78.3 (15.4)	65.6 (14.0)	<0.0001
HbA1c (%)	9.3 (1.4)	8.2 (1.3)	
Weight (kg)	106.1 (17.9)	97.9 (23.0)	<0.0001
BMI (kg/m^2)	38.4 (8.3)	35.0 (7.6)	<0.0001

BMI: Body mass index. Mean and standard deviation shown for normal data and analysed by paired t-test.

Figure 1: Diabetes therapies used by patients in our cohort prior to the initiation of dapagliflozin



References

1. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. *The New England journal of medicine*. 2019;380:347-357.

2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *The New England journal of medicine*. 2017;377:644-657.

3. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *The New England journal of medicine*. 2015;373:2117-28.

4. Heerspink HJL, Karasik A, Thuresson M, et al. Kidney outcomes associated with use of SGLT2 inhibitors in real-world clinical practice (CVD-REAL 3): a multinational observational cohort study. *The lancet Diabetes & endocrinology*. 2020;8:27-35.

5. Woo V, Bell A, Clement M, et al. CANadian CAnagliflozin REgistry: Patient-Reported Outcomes of Canagliflozin in the Treatment of Type 2 Diabetes Mellitus in Canadian Clinical Practice. *Canadian journal of diabetes*. 2019;43:464-471.

6. Shao SC, Chang KC, Hung MJ, et al. Comparative risk evaluation for cardiovascular events associated with dapagliflozin vs. empagliflozin in real-world type 2 diabetes patients: a multi-institutional cohort study. *Cardiovascular diabetology*. 2019;18:120.

7. Canivell S, Mata-Cases M, Vlacho B, et al. How Many Patients with Type 2 Diabetes Meet the Inclusion Criteria of the Cardiovascular Outcome Trials with SGLT2 Inhibitors? Estimations from a Population Database in a Mediterranean Area. *Journal of diabetes research*. 2019;2019:2018374.

8. Fadini GP, Tentolouris N, Caballero Mateos I, Bellido Castaneda V and Morales Portillo C. A Multinational Real-World Study on the Clinical Characteristics of Patients with Type 2 Diabetes Initiating Dapagliflozin in Southern Europe. *Diabetes therapy : research, treatment and education of diabetes and related disorders*. 2019.

9. Carretero Gomez J, Arevalo Lorido JC, Gomez Huelgas R, et al. Combination Therapy With Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors in Older Patients With Type 2 Diabetes: A Real-World Evidence Study. *Canadian journal of diabetes*. 2019;43:186-192.

10. Castellana M, Cignarelli A, Brescia F, et al. Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis. *Scientific reports*. 2019;9:19351.

11. Mirabelli M, Chiefari E, Caroleo P, et al. Long-Term Effectiveness and Safety of SGLT-2 Inhibitors in an Italian Cohort of Patients with Type 2 Diabetes Mellitus. *Journal of diabetes research*. 2019;2019:3971060.

12. Jabbour S. Durability of response to dapagliflozin: a review of long-term efficacy and safety. *Current medical research and opinion*. 2017;33:1685-1696.

13. Nicolucci A, Candido R, Cucinotta D, et al. Generalizability of Cardiovascular Safety Trials on SGLT2 Inhibitors to the Real World: Implications for Clinical Practice. *Advances in therapy*. 2019;36:2895-2909.